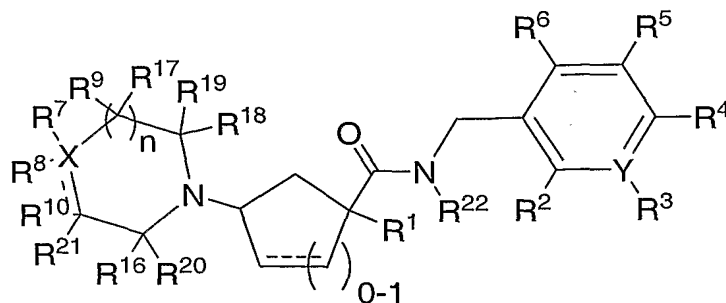


WHAT IS CLAIMED IS:

1. A compound of Formula I:



I

wherein:

X is C, N, O, S or SO₂;

Y is N or C;

R¹ is selected from: hydrogen, -SO₂R¹⁴, -C₀₋₃alkyl-S(O)R¹⁴, -SO₂NR¹²R¹², -C₁₋₆alkyl, -C₀₋₆alkyl-O-C₁₋₆alkyl, -C₀₋₆alkyl-S-C₁₋₆alkyl, -(C₀₋₆alkyl)-(C₃₋₇cycloalkyl)-(C₀₋₆alkyl), hydroxy, heterocycle, -CN, -NR¹²R¹², -NR¹²COR¹³, -NR¹²SO₂R¹⁴, -COR¹¹, -CONR¹²R¹², and phenyl,

where said alkyl and said cycloalkyl are unsubstituted or substituted with 1-7 substituents independently selected from: halo, hydroxy, -O-C₁₋₃alkyl, trifluoromethyl, C₁₋₃alkyl, -O-C₁₋₃alkyl, -COR¹¹, -SO₂R¹⁴, -NHCOCH₃, -NHCO₂CH₃, -heterocycle, =O, and -CN,

where said phenyl and said heterocycle are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy and trifluoromethyl;

R² is selected from: hydrogen, C₁₋₃alkyl unsubstituted or substituted with 1-3 fluoro, -O-C₁₋₃alkyl unsubstituted or substituted with 1-3 fluoro, hydroxy, chloro, fluoro, bromo, phenyl and heterocycle;

R³ is selected from: hydrogen, hydroxy, halo, C₁₋₃alkyl unsubstituted or substituted with 1-6 substituents independently selected from fluoro, hydroxy, and -COR¹¹, -NR¹²R¹², -COR¹¹, -CONR¹²R¹², -NR¹²COR¹³, -OCONR¹²R¹², -NR¹²CONR¹²R¹², -heterocycle, -CN, -NR¹²-SO₂-NR¹²R¹², -NR¹²-SO₂-R¹⁴, -SO₂-NR¹²R¹² and nitro, when Y is C; or

5

R³ is oxygen or is absent, when Y is N;

R⁴ is selected from: hydrogen, C₁₋₆alkyl, trifluoromethyl, trifluoromethoxy, chloro, fluoro, bromo, and phenyl;

10

R⁵ is selected from: C₁₋₆alkyl unsubstituted or substituted with one or more substituents selected from 1-6 fluoro and hydroxyl, -O-C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, -CO-C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, -S-C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, -pyridyl unsubstituted or substituted with one or more substituents selected from halo, trifluoromethyl, C₁₋₄alkyl and COR¹¹, fluoro, chloro, bromo, -C₄₋₆cycloalkyl, -O-C₄₋₆cycloalkyl, phenyl unsubstituted or substituted with one or more substituents selected from halo, trifluoromethyl, C₁₋₄alkyl and COR¹¹, -O-phenyl unsubstituted or substituted with one or more substituents selected from halo, trifluoromethyl, C₁₋₄alkyl and COR¹¹, -C₃₋₆cycloalkyl unsubstituted or substituted with 1-6 fluoro, -O-C₃₋₆cycloalkyl unsubstituted or substituted with 1-6 fluoro, -heterocycle, -CN and -COR¹¹;

15

20

R⁶ is selected from: hydrogen, C₁₋₆alkyl, trifluoromethyl, fluoro, chloro and bromo;

R⁷ is nothing when X is -O-, -S-, or -SO₂-;

25

R⁷ is selected from: hydrogen, (C₀₋₆alkyl)-phenyl, (C₀₋₆alkyl)-heterocycle, (C₀₋₆alkyl)-C₃₋₇cycloalkyl, (C₀₋₆alkyl)-COR¹¹, (C₀₋₆alkyl)-(alkene)-COR¹¹, (C₀₋₆alkyl)-SO₃H, (C₀₋₆alkyl)-W-C₀₋₄alkyl, (C₀₋₆alkyl)-CONR¹²-phenyl and (C₀₋₆alkyl)-CONR¹⁵-V-COR¹¹, when X is C or N,

where V is selected from C₁₋₆alkyl and phenyl,

30

where W is selected from: a single bond, -O-, -S-, -SO-, -SO₂-, -CO-, -CO₂-, -CONR¹²- and -NR¹²-,

where said C₀₋₆alkyl is unsubstituted or substituted with 1-5 substituents independently selected from: halo, hydroxy, -C₀₋₆alkyl, -O-C₁₋₃alkyl, trifluoromethyl and -C₀₋₂alkyl-phenyl,

where said alkene is unsubstituted or substituted with 1-3 substituents independently selected from: halo, trifluoromethyl, C₁₋₃alkyl, phenyl and heterocycle;

where said phenyl, heterocycle, cycloalkyl and C₀₋₄alkyl are independently unsubstituted or substituted with 1-5 substituents independently selected from: halo, trifluoromethyl, hydroxy, C₁₋₆alkyl, -O-C₁₋₃alkyl, -C₀₋₃-COR¹¹, -CN, -NR¹²R¹², -CONR¹²R¹² and -C₀₋₃-heterocycle,

or where said phenyl and heterocycle are fused to another heterocycle, which itself may be unsubstituted or substituted with 1-2 substituents independently selected from hydroxy, halo, -COR¹¹, and -C₁₋₄alkyl;

R⁸ is selected from: hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyl-hydroxy, -O-C₁₋₃alkyl, -COR¹¹, -CONR¹²R¹² and -CN, when X is C, or;

R⁸ is nothing when X is O, S, SO₂ or N, or when a double bond joins the carbons to which R⁷ and R¹⁰ are attached;

or R⁷ and R⁸ are joined together to form a ring which is selected from: 1H-indene, 2,3-dihydro-1H-indene, 2,3-dihydro-benzofuran, 1,3-dihydro-isobenzofuran, 2,3-dihydro-benzothiofuran, 1,3-dihydro-isobenzothiofuran, 6H-cyclopenta[*d*]isoxazol-3-ol, cyclopentane and cyclohexane,

where said ring is unsubstituted or substituted with 1-5 substituents independently selected from: halo, trifluoromethyl, hydroxy, C₁₋₃alkyl, -O-C₁₋₃alkyl, -C₀₋₃-COR¹¹, -CN, -NR¹²R¹², -CONR¹²R¹² and -C₀₋₃-heterocycle;

R⁹ and R¹⁰ are independently selected from: hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyl-COR¹¹, C₁₋₆alkyl-hydroxy, -O-C₁₋₃alkyl, =O when R⁹ or R¹⁰ is connected to the ring via a double bond and halo;

or R⁷ and R⁹, or R⁸ and R¹⁰, are joined together to form a ring which is phenyl or heterocycle,

5

where said ring is unsubstituted or substituted with 1-7 substituents independently selected from: halo, trifluoromethyl, hydroxy, C₁₋₃alkyl, -O-C₁₋₃alkyl, -COR¹¹, -CN, -NR¹²R¹² and -CONR¹²R¹²;

10 R¹¹ is independently selected from: hydroxy, hydrogen, C₁₋₆ alkyl, -O-C₁₋₆alkyl, benzyl, phenyl, C₃₋₆ cycloalkyl,

where said alkyl, phenyl, benzyl or cycloalkyl group is unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-

15

C₁₋₆ alkyl, and trifluoromethyl;

R¹² is selected from: hydrogen, C₁₋₆ alkyl, benzyl, phenyl and C₃₋₆ cycloalkyl,

where said alkyl, phenyl, benzyl or cycloalkyl group is unsubstituted or substituted with 1-3

20

substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂- C₁₋₆ alkyl and trifluoromethyl;

R¹³ is selected from: hydrogen, C₁₋₆ alkyl, -O-C₁₋₆alkyl, benzyl, phenyl and C₃₋₆ cycloalkyl,

25

where said alkyl, phenyl, benzyl or cycloalkyl group is unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂- C₁₋₆ alkyl, and trifluoromethyl;

R¹⁴ is selected from: hydroxy, C₁₋₆ alkyl, -O-C₁₋₆alkyl, benzyl, phenyl and C₃₋₆ cycloalkyl,

30

where said alkyl, phenyl, benzyl or cycloalkyl group is unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl and trifluoromethyl;

5 R¹⁵ is hydrogen or C₁₋₄alkyl, or R¹⁵ is joined via a 1-5 carbon tether to one of the carbons of V to form a ring;

R¹⁷, R¹⁹, R²⁰ and R²¹ are independently selected from: hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyl-COR¹¹, C₁₋₆alkyl-hydroxy, -O-C₁₋₃alkyl, trifluoromethyl and halo;

10

R¹⁶ and R¹⁸ are independently selected from: hydroxy, C₁₋₆alkyl, C₁₋₆alkyl-COR¹¹, C₁₋₆alkyl-hydroxy, -O-C₁₋₃alkyl and halo,

15

where said alkyl is unsubstituted or substituted with 1-6 substituents independently selected from fluoro and hydroxyl;

20

or R¹⁶ and R¹⁸ together form a bridge consisting of -C₁₋₄alkyl-, -C₀₋₂alkyl-O-C₁₋₃alkyl- or -C₁₋₃alkyl-O-C₀₋₂alkyl-, where said alkyl is unsubstituted or substituted with 1-2 substituents independently selected from: oxy where the oxygen is joined to said bridge via a double bond, fluoro, hydroxy, methoxy, methyl and trifluoromethyl;

R²² selected from: hydrogen, phenyl, C₁₋₆alkyl which is substituted or unsubstituted with 1-6 substituents selected from: -COR¹¹, hydroxy, fluoro, chloro and -O-C₁₋₃alkyl;

25

or R² and R²² together are a linker, forming a heterocycle ring, said linker selected from (with the left side of the linker being bonded to the amide nitrogen at R²²): -CH₂(CR²³R²³)₁₋₃-, -CH₂-NR²⁴-, -NR¹²-CR²³R²³-, -CH₂O-, -CH₂SO₂-, -CH₂SO-, -CH₂S-, -CR²³R²³-;

30

R²³ is independently selected from: hydrogen, C₁₋₃alkyl unsubstituted or substituted with 1-6 substituents independently selected from fluoro and hydroxy, COR¹³, SO₂R¹⁴, SO₂NR¹²R¹², hydroxy, halo, -NR¹²R¹², -COR¹¹, -CONR¹²R¹², -NR¹²COR¹³, -OCONR¹²R¹², -NR¹²CONR¹²R¹², -heterocycle, -CN, -NR¹²-SO₂-NR¹²R¹², -NR¹²-SO₂-R¹⁴, and -SO₂-NR¹²R¹²;

or one R^{23} is =O and the other R^{23} is absent;

where R^{24} is selected from: hydrogen, C_{1-3} alkyl where said alkyl is unsubstituted or substituted with 1-6 substituents independently selected from fluoro and hydroxy, COR^{13} , SO_2R^{14} and $SO_2NR^{12}R^{12}$;

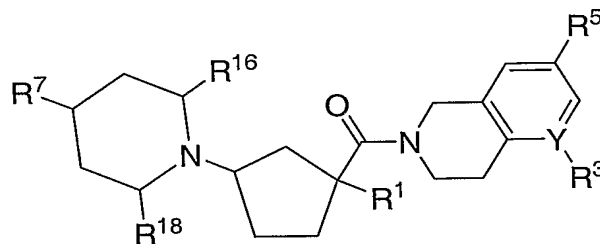
n is selected from 0, 1 and 2;

the dashed line represents an optional bond;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

2. The compound of claim 1, wherein R^{16} and R^{18} together form a bridge consisting of $-C_{1-4}$ alkyl-, $-C_{0-2}$ alkyl-O- C_{1-3} alkyl- or $-C_{1-3}$ alkyl-O- C_{0-2} alkyl-, where said alkyl is unsubstituted or substituted with 1-2 substituents independently selected from: oxy where the oxygen is joined to said bridge via a double bond, fluoro, hydroxy, methoxy, methyl and trifluoromethyl.

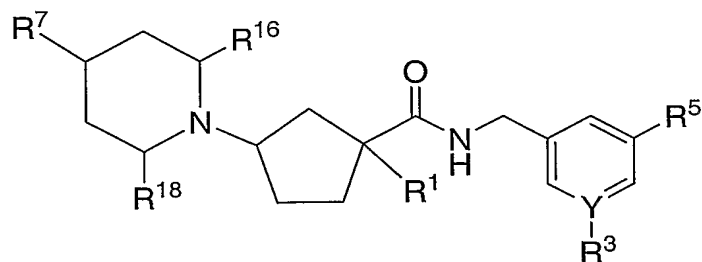
3. The compound of claim 1 of the Formula Ia:



Ia

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

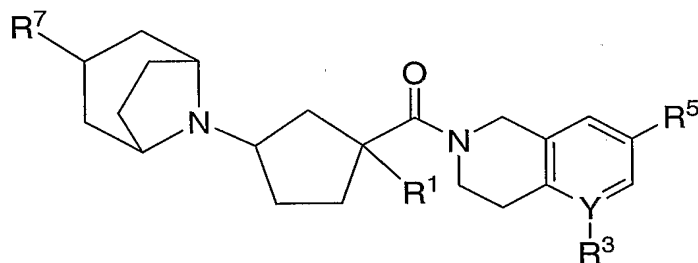
4. The compound of claim 1 of the Formula Ib:



Ib

- 5 and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

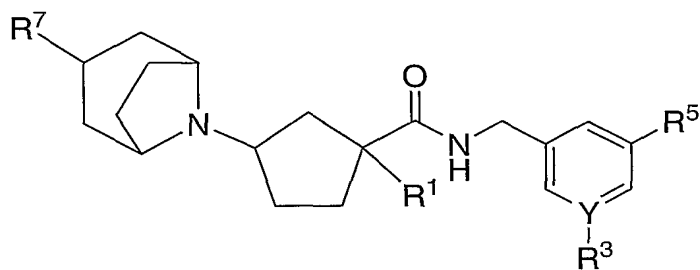
5. The compound of claim 1 of the Formula Ic:



Ic

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

6. The compound of claim 1 of the Formula Id:

**Id**

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

5

7. The compound of claim 1, wherein R^1 is C_{1-6} alkyl, unsubstituted or substituted with hydroxyl or 1-6 fluoro, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

10

8. The compound of claim 6, wherein R^1 is selected from: $-CH(CH_3)_2$, $-CH(OH)CH_3$ and $-CH_2CF_3$, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

15

9. The compound of claim 1, wherein R^2 is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

10. The compound of claim 1, wherein R^2 is connected to R^{22} by $-CH_2-CH_2-$, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

20

11. The compound of claim 1, wherein, when Y is N, R^3 is absent, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

12. The compound of claim 1, wherein, when Y is N, R^3 is O, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

25

13. The compound of claim 1, wherein, when Y is C, R³ is selected from: hydrogen, halo, hydroxyl, C₁₋₃alkyl where said alkyl is unsubstituted or substituted with 1-6 substituents independently selected from fluoro and hydroxy, -COR¹¹, -CONR¹²R¹², -heterocycle, -NR¹²-SO₂-NR¹²R¹², -NR¹²-SO₂-R¹⁴, -SO₂-NR¹²R¹², -nitro and -NR¹²R¹², and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

14. The compound of claim 12, wherein R³ is hydrogen, fluoro, or trifluoromethyl, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

15. The compound of claim 1, wherein R⁴ is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

16. The compound of claim 1, wherein R⁵ is selected from: C₁₋₆alkyl substituted with 1-6 fluoro, -O-C₁₋₆alkyl substituted with 1-6 fluoro, chloro, bromo and phenyl, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

17. The compound of claim 15, wherein R⁵ is trifluoromethyl, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

18. The compound of claim 1, wherein R⁶ is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

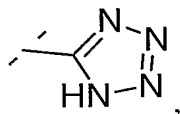
19. The compound of claim 1, wherein R⁷ is phenyl, heterocycle, C₃₋₇cycloalkyl, C₁₋₆alkyl, -COR¹¹ or -CONH-V-COR¹¹, where V is C₁₋₆alkyl or phenyl, where said phenyl, heterocycle, C₃₋₇cycloalkyl and C₁₋₆alkyl are unsubstituted or substituted with 1-5 substituents independently selected from: halo, trifluoromethyl, hydroxy, C₁₋₃alkyl, -O-C₁₋₃alkyl, -COR¹¹, -CN, -heterocycle and -CONR¹²R¹², and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

20. The compound of claim 1, wherein R⁷ is phenyl, heterocycle, C₁₋₄alkyl, -COR¹¹, and -CONH-V-COR¹¹, where V is selected from C₁₋₆alkyl or phenyl, and where the phenyl, heterocycle, and C₁₋₄alkyl is unsubstituted or substituted with 1-3 substituents independently selected

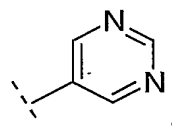
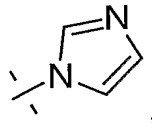
from: halo, hydroxy, C₁₋₃alkyl, -O-C₁₋₃alkyl, -COR¹¹ and -heterocycle, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

21. The compound of claim 1, wherein, when X is C, R⁷ is selected from:

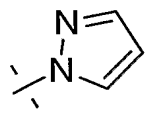
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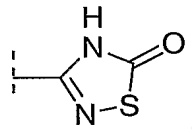
para-fluorophenyl,



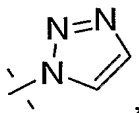
3-carboxyphenyl,



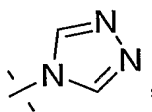
3-carboxy-4-fluorophenyl,



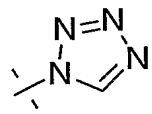
phenyl,



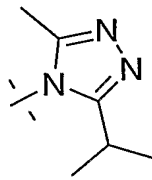
-CO₂CH₂CH₃,



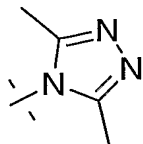
-CO₂H,



-CONHCH₃,



-hydroxy, and



and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

22. The compound of claim 1, wherein, when X is C, R⁸ is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

23. The compound of claim 1, wherein R⁹ and R¹⁰ are hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

24. The compound of claim 1, wherein R¹⁶ is selected from: methyl, fluoro and trifluoromethyl, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

25. The compound of claim 1, wherein R¹⁷ is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

26. The compound of claim 1, wherein R¹⁸ is selected from: methyl, fluoro and trifluoromethyl, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

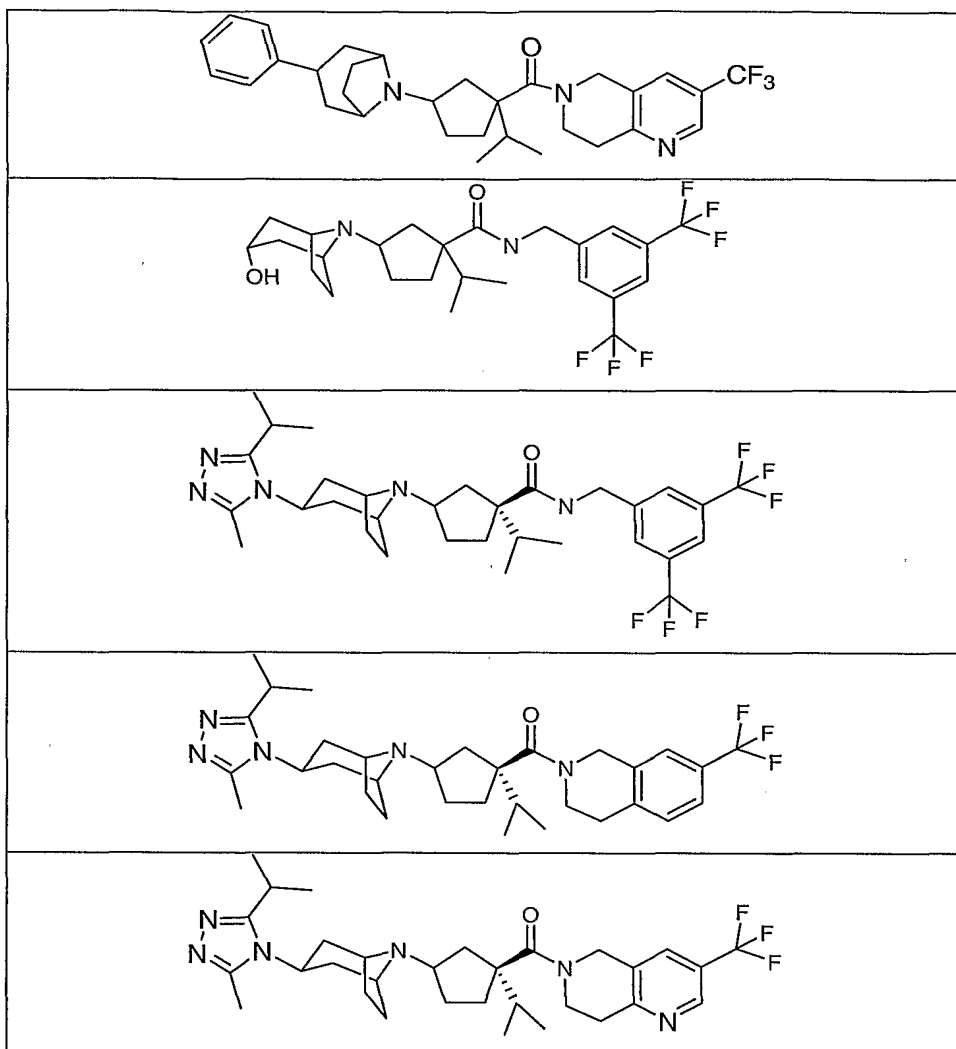
27. The compound of claim 1, wherein R¹⁶ and R¹⁸ are joined by -CH₂-CH₂- to make a 5 membered heterocycle, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

28. The compound of claim 1, wherein one or more of R¹⁹, R²⁰, R²¹ and R²² is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

29. The compound of claim 1, wherein R²² is connected to R² together form a -CH₂-CH₂- bridge, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

30. The compound of claim 1, wherein n is 1, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

31. A compound selected from:



5 and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

32. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

10 33. A method for modulations of chemokine receptor activity in a mammal which comprises the administration of an effective amount of a compound of Claim 1.

34. A method for treating, ameliorating, controlling or reducing the risk of an inflammatory and immunoregulatory disorder or disease which comprises the administration to a patient of an effective amount of a compound of Claim 1.

5 35. A method for treating, ameliorating, controlling or reducing the risk of rheumatoid arthritis which comprises the administration to a patient of an effective amount of a compound of Claim 1.